AMERICAN THORACIC SOCIETY DOCUMENTS

Official American Thoracic Society Clinical Practice Guidelines: Diagnostic Evaluation of Infants with Recurrent or Persistent Wheezing

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Background: Infantile wheezing is a common problem, but there are no guidelines for the evaluation of infants with recurrent or persistent wheezing that is not relieved or prevented by standard therapies.

Methods: An American Thoracic Society–sanctioned guideline development committee selected clinical questions related to uncertainties or controversies in the diagnostic evaluation of wheezing infants. Members of the committee conducted pragmatic evidence syntheses, which followed the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. The evidence syntheses were used to inform the formulation and grading of recommendations.

Results: The pragmatic evidence syntheses identified few studies that addressed the clinical questions. The studies that were identified constituted very low-quality evidence, consisting almost exclusively of case series with risk of selection bias, indirect patient populations, and imprecise estimates. The committee made conditional recommendations to perform bronchoscopic airway survey, bronchoalveolar lavage, esophageal pH monitoring, and a swallowing study. It also made conditional recommendations against empiric food avoidance, upper gastrointestinal radiography, and gastrointestinal scintigraphy. Finally, the committee recommended additional research about the roles of infant pulmonary function testing and food avoidance or dietary changes, based on allergy testing.

Conclusions: Although infantile wheezing is common, there is a paucity of evidence to guide clinicians in selecting diagnostic tests for recurrent or persistent wheezing. Our committee made several conditional recommendations to guide clinicians; however, additional research that measures clinical outcomes is needed to improve our confidence in the effects of various diagnostic interventions and to allow advice to be provided with greater confidence.

Overview

Wheezing occurs commonly during infancy (1). In most cases, wheezing episodes are mild and easily treated (2). However, some infants will develop persistent or recurrent wheezing, which is often severe (3). These infants are frequently referred to pediatric pulmonology specialists for further evaluation and treatment. Guidelines for diagnostic testing exist for older children with asthma (4), but such guidelines are lacking for wheezing infants. In a 2009 survey of Assembly on Pediatrics members of the American Thoracic Society (ATS), infantile wheezing was one of the highest ranked topics for which members desired a guideline. To address this knowledge gap and interest, the ATS convened a committee of pediatric pulmonologists with clinical and research experience in infantile wheezing to develop evidence-based guidelines for the diagnostic evaluation of infantile wheezing.

For these guidelines, the committee defined infantile wheezing as recurrent or persistent episodes of wheezing in infants

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less than 24 months old (herein referred to as "infants with persistent wheezing"). The guidelines address diagnostic tests that are frequently considered by pediatric pulmonologists and other clinicians when evaluating infantile wheezing, but are either controversial or a frequent source of uncertainty. Diagnostic tests that are generally considered standard of care (e.g., chest radiography) were not addressed.

The committee performed a pragmatic evidence synthesis and then used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach (5) to formulate and grade the following recommendations:

1. For infants with persistent wheezing despite treatment with bronchodilators, inhaled corticosteroids, or systemic corticosteroids, we suggest an airway survey via flexible fiberoptic bronchoscopy (conditional recommendation, very low quality of evidence).
2. For infants with persistent wheezing despite treatment with bronchodilators, inhaled corticosteroids, or systemic corticosteroids, we suggest bronchoalveolar lavage (BAL) (conditional recommendation, very low quality of evidence).
3. We recommend research studies in infants with persistent wheezing despite treatment with bronchodilators, inhaled corticosteroids, or systemic corticosteroids, which compare clinical outcomes among those who are managed according to results of infant pulmonary function testing using the raised-volume rapid thoracoabdominal compression (RVRTC) method versus those who are managed according to clinical assessment alone.
4. A. For infants who do not have eczema but have persistent wheezing despite treatment with bronchodilators, inhaled corticosteroids, or systemic corticosteroids, we suggest that clinicians and caregivers *not* use empiric food avoidance or dietary changes (conditional recommendation, very low quality of evidence).
   B. We recommend research studies that determine whether food avoidance or dietary changes guided by food allergy testing improves clinical outcomes in infants who do not have eczema but have persistent wheezing despite treatment with bronchodilators, inhaled corticosteroids, or systemic corticosteroids.
5. For infants with persistent wheezing despite treatment with bronchodilators, inhaled corticosteroids, or systemic corticosteroids, we suggest 24-hour esophageal pH monitoring (conditional recommendation, very low quality of evidence).
6. For infants with persistent wheezing despite treatment with bronchodilators, inhaled corticosteroids, or systemic corticosteroids, we suggest 24-hour esophageal pH monitoring rather than upper gastrointestinal radiography (conditional recommendation, very low quality of evidence).
7. For infants with persistent wheezing despite treatment with bronchodilators, inhaled corticosteroids, or systemic corticosteroids, we suggest 24-hour esophageal pH monitoring rather than gastrointestinal scintigraphy (conditional recommendation, very low quality of evidence).
8. For infants with persistent wheezing despite treatment with bronchodilators, inhaled corticosteroids, or systemic corticosteroids, we suggest performing video-fluoroscopic swallowing studies (conditional recommendation, very low quality of evidence).

Introduction

Wheezing during infancy is a common clinical problem. In the Tucson Children's Respiratory Study, a longitudinal birth cohort study of healthy full-term infants,

34% of children had at least one episode of wheezing before age 3 years (1). In some infants, this is a sign of early-onset asthma (6), whereas other infants may wheeze because of diminished airway function or innate immune responses (7, 8). For the majority of infants, these wheezing episodes are mild, episodic, and easily treated. However, some infants will develop severe recurrent or persistent wheezing. Guidelines for the evaluation and treatment of asthma in older children and the general approach to the evaluation of infantile wheezing have been published (4, 9), but no guidelines exist for the use of more specialized testing, such as flexible fiberoptic bronchoscopy, in the evaluation of infants with persistent wheezing. Recognizing the need for clinical guidance on the diagnostic evaluation of wheezing infants, the ATS convened a guideline development committee of pediatric specialists to conduct pragmatic evidence syntheses and then use the evidence syntheses as the basis for recommendations for the evaluation of persistent wheezing in infancy.

Use of These Guidelines

These ATS guidelines are not meant to establish a standard of care. Rather, they represent an effort to summarize evidence and provide reasonable clinical recommendations based on that evidence. Clinicians, patients, third-party payers, other stakeholders, and the courts should never view these recommendations as dictates. No guidelines or recommendations can take into account all of the often compelling, unique individual clinical circumstances. Therefore, no one charged with evaluating clinicians' actions should attempt to apply the recommendations from these guidelines by rote or in a blanket fashion. These guidelines are not intended to be a comprehensive review of the evaluation of infantile wheezing, but rather to provide evidence-based recommendations for a set of specialized diagnostic tests frequently considered in the evaluation of this patient population. Clinicians will be able to use these recommendations when considering specific diagnostic tests for the evaluation of persistent wheezing. Recommendations for order or selection of diagnostic testing are beyond the scope of this document, and such decisions will vary depending on the specific clinical situation and parent preferences.

Methods

Definition

For these guidelines, the committee defined infantile wheezing as recurrent or persistent episodes of wheezing in infants less than 24 months old (herein, referred to as "infants with persistent wheezing"). This cutoff was chosen for two reasons: previous documents have addressed wheezing in preschool-aged children (3–5 yr old) (10), and wheezing on the basis of diminished airway function tends to improve by age 3 years (1). The population was further limited to infants with persistent wheezing despite treatment with recommended first-line therapies of bronchodilators, inhaled corticosteroids, or systemic corticosteroids (11).

Process

The co-chairs (C.L.R. and C.R.E.) were confirmed by the ATS Assembly on Pediatrics, Program Review Subcommittee, and Board of Directors. A guideline development committee was then assembled, which consisted of pediatric clinicians and researchers with expertise in the evaluation of wheezing during infancy. All members of the committee disclosed and were vetted for potential conflicts of interest according to the rules and procedures of the ATS. The committee then developed clinical questions, using the PICO (Patient, Intervention, Comparator, and Outcomes) framework. Each question was the basis of a pragmatic evidence synthesis, which consisted of searching the Medline and CINAHL (Cumulative Index to Nursing and Allied Health Literature) databases on the basis of prespecified search criteria, selecting studies based on prespecified selection criteria, and appraising and summarizing the evidence according to the GRADE approach. The evidence syntheses were used as the basis for the formulation of recommendations, which was based on consideration of the balance of benefits versus harms and burdens, quality of evidence, patient preferences, and cost and resource use. The recommendations were graded according to the GRADE approach. The specifics of the PICO framework, outcomes, and other methods are described in greater detail in the online supplement.

Results

Question 1: Should Infants with Persistent Wheezing despite Treatment with Bronchodilators, Inhaled Corticosteroids, or Systemic Corticosteroids Undergo Airway Survey via Flexible Fiberoptic Bronchoscopy?

Summary of evidence. Our literature search did not identify any studies that compared wheezing infants undergoing airway survey via bronchoscopy with wheezing infants who did not undergo airway survey. Therefore, our recommendation is based on 10 case series that collectively included 1,364 patients and reported that 452 of the 1,364 patients (33%) who underwent airway survey for respiratory symptoms were found to have an anatomic abnormality known to cause wheezing (Table 1) (12–21). Lesions included tracheomalacia, bronchomalacia, tracheobronchomalacia, vascular rings, vascular slings, and airway compression by a vascular structure. No major complications were reported in any of the case series, with minor complications such as transient hypoxemia described in 5–10% of subjects.

Infants with wheezing due to tracheomalacia, bronchomalacia, or tracheobronchomalacia are typically managed by observation alone if wheezing is the only abnormality or the associated symptoms are mild, because the vast majority of infants improve over time with conservative therapy (22). Infants with wheezing due to tracheomalacia, bronchomalacia, or tracheobronchomalacia occasionally require an intervention (e.g., positive airway pressure, surgery, or stenting) because of accompanying life-threatening airway obstruction, respiratory failure, recurrent pneumonias, or failure to thrive. Positive airway pressure immediately decreases respiratory distress, restores airway patency, and improves pulmonary function according to multiple small case series and case reports (23–30). Surgery (most commonly, aortopexy) relieves obstruction in virtually all patients with tracheomalacia, but is less effective in patients with tracheobronchomalacia or bronchomalacia according to small case series (31–37). This was illustrated by a case series in which 21 of 21 patients (100%) had tracheomalacia corrected by aortopexy, but only 1 of 4 patients (25%) with

Table 1. Airway Survey: Quality Assessment and Summary of Findings

Quality Assessment									
No.	**Study Design**	**Limitations**	**Indirectness**	**Inconsistency**	**Imprecision**	**Publication Bias**	**Importance of Outcome**	**Quality of Evidence**	**Summary of Findings**
Frequency with which bronchoscopy identifies an anatomical lesion known to cause wheezing									
10*	Case series†	Serious‡	Serious§	None	Serious‖	Undetected	Not a prespecified outcome	Very low	The 10 case series collectively included 1,364 patients. 452 of 1,364 patients (33%) were found to have anatomical abnormalities known to cause wheezing. The largest series included 885 patients. When this study was removed, the estimate was unchanged. Complications were rarely reported.
Frequency of wheezing after treatment									
27¶	Case series† and case reports	Serious**	Serious††	None	Serious‡‡	Undetected	Critical	Very low	90% of patients with tracheomalacia, bronchomalacia, or tracheobronchomalacia improved with time alone. 88–100% of patients with vascular rings, vascular slings, or vascular compression of the airways improved with surgery. Complications occurred in 10% and mortality in <5%.

*References 12–21.
†No studies included a control group. Therefore, they are all case series.
‡Limitations were serious because of probable selection bias related to who underwent bronchoscopy and who did not. Most studies did not provide details of how they decided when to perform bronchoscopy with airway survey and when not to perform bronchoscopy with airway survey.
§Indirectness was serious because few studies were limited solely to wheezing infants. Most included infants with respiratory symptoms or signs, such as stridor, wheezing, cough, respiratory distress or failure, or recurrent infections.
‖Imprecision was serious because sample size was small (<100) in all but one of the studies that were reviewed.
¶References 23–42 and 44–50.
**Limitations were serious because of probable selection bias related to who was eventually treated with positive airway pressure, airway stenting, and surgery, as well as which type of surgery was used.
††Indirectness was serious because few studies were limited solely to wheezing infants. Most included infants being treated for a variety of respiratory symptoms or signs (e.g., stridor, wheezing, cough, respiratory distress or failure, or recurrent infections) caused by anatomical abnormalities.
‡‡Imprecision was serious because the sample size was small (<100) in all the studies that were reviewed.

tracheobronchomalacia was corrected by aortopexy (31). Airway stenting has been used to improve airway obstruction in infants (38–42), but complications including formation of granulation tissue, migration, or erosion occurred in 50% of cases and were potentially associated with death in 2 of 22 infants (39, 40). Newer approaches include direct tracheobronchopexy (43).

In contrast, wheezing due to vascular rings, vascular slings, and airway compression by a vascular structure is unlikely to self-resolve, and surgical correction is performed for symptomatic patients. According to seven case series, improvement in respiratory symptoms was seen in 88–100% of patients, and complete resolution was seen in more than 50% of patients. Recurrent laryngeal nerve injury was the most common surgical complication and occurred in less than 10% of patients. More serious complications such as aortoesophageal fistula, heart failure, or wound infection associated with mortality occurred in less than 5% of patients (44–50).

Taken together, the evidence indicates that an anatomic abnormality known to cause wheezing can be identified by airway survey in approximately 33% of patients with respiratory symptoms, and in the committee's clinical experience more than 90% of such patients will improve because either their condition is self-limited or surgery can correct the abnormality. Thus, about 30% of patients are likely to benefit from an airway survey, either through direct intervention (surgery) or by avoiding unnecessary tests and treatments for a benign, self-limited condition. Identification of airway malacia may also help in management of infants believed to have concomitant asthma, because β-agonists may adversely affect airway dynamics in these children (51). The committee has very low confidence (i.e., quality of evidence) in the accuracy of these estimated effects, because the case series had probable selection bias and most series looked at infants who underwent bronchoscopy for respiratory symptoms, not specifically wheezing.

Rationale. Bronchoscopy with airway survey that identifies an anatomical cause of wheezing confers several potential benefits. Finding tracheomalacia, bronchomalacia, or tracheobronchomalacia usually leads to conservative management, which has a high success rate and other benefits including relief from the burden, cost, and potential harms of further diagnostic testing; probable reductions in the use of ineffective medications (bronchodilators or systemic corticosteroids) and the frequency of physician visits; and parental reassurance, given the high likelihood that the condition will spontaneously resolve. Finding vascular rings, vascular slings, and airway compression by a vascular structure leads to surgical therapy with an 88–100% success rate. In the judgment of the committee, the possibility that approximately 30% of infants who undergo airway survey will benefit far exceeds the burdens and cost of bronchoscopy, as well as the potential harms (i.e., complications due to bronchoscopy are rare and complications due to subsequent therapy range from zero for conservative management to approximately 10% for surgery). The recommendation for airway survey is conditional because the low quality of evidence provides little certainty that the benefits of airway survey exceed the burdens, costs, and harms. There are also emerging data on neurodevelopmental risks of anesthesia that need to be considered (52). In addition, parental preferences regarding invasive procedures tend to be highly individualized.

Recommendation 1. For infants with persistent wheezing despite treatment with bronchodilators, inhaled corticosteroids, or systemic corticosteroids, we suggest airway survey via flexible fiberoptic bronchoscopy (conditional recommendation, very low quality of evidence).

Question 2: Should Infants with Persistent Wheezing despite Treatment with Bronchodilators, Inhaled Corticosteroids, or Systemic Corticosteroids Undergo Bronchoalveolar Lavage?

Summary of evidence. Our literature search did not identify any studies that compared wheezing infants undergoing BAL with wheezing infants who did not undergo BAL. Therefore, our recommendation is based on data from 20 case series, identified in our literature search, showing that 14–80% of infants (40–60% in most studies) with recurrent or persistent wheezing produce a positive BAL culture (Table 2) (12, 16, 18, 53–70). No complications were reported in any of the case series.

Patients with a positive BAL culture typically receive a prolonged course of antibiotic therapy, and indirect evidence from a randomized trial of 50 children with productive cough presumed to be caused by bacterial bronchitis found that the cough resolved in 48% of children who received antibiotic therapy, compared with only 16% of those who did not receive antibiotics (71). The trial likely underestimated the effects of antibiotics in patients with bacterial bronchitis because children did not need to have a confirmed bacterial infection to be enrolled in the trial; patients without bacterial bronchitis are unlikely to have responded to antibiotic therapy and, therefore, their inclusion would have made antibiotic therapy appear less effective.

On the basis of the rates of BAL infection (40–60%) and symptom improvement with antibiotic treatment (48%) described previously, we estimate that 20–30% of children with persistent wheezing who undergo bronchoscopy with BAL will be found to have a lower airway bacterial infection and that their symptoms will improve with antibiotic therapy. The committee's confidence in the estimated effects of BAL (i.e., the quality of evidence) is very low because it is based on prevalence estimates derived from case series and a therapeutic effect estimated from a randomized trial, both of which had serious limitations. The case series were limited by selection bias, indirectness of the population (children with cough rather than infants with wheezing), and small sample sizes with few events. The randomized trial was similarly limited by indirectness of the population (children with cough rather than infants with wheezing), indirectness of the outcome (cure of infection rather than improvement in wheezing), and imprecision (small sample size with few events).

Rationale. To confirm or exclude lower airway bacterial infection as the cause of recurrent or persistent wheezing, clinicians have three options: (*1*) they can perform BAL and then treat patients with confirmed bacterial infection with antibiotics; (*2*) they can empirically treat all patients with empiric antibiotics; or (*3*) they can do neither. The committee judged the balance of the benefits versus the burdens and risks to be greater for the first option (i.e., 20–30% children improve after treatment of BAL-identified infection) than for either the second option (i.e., the same infection cure rate, but 40–60% of patients receive unnecessary antibiotics

Table 2. Bronchoalveolar Lavage: Quality Assessment and Summary of Findings

Quality Assessment									
No.	**Study Design**	**Limitations**	**Indirectness**	**Inconsistency**	**Imprecision**	**Publication Bias**	**Importance of Outcome**	**Quality of Evidence**	**Summary of Findings**
Frequency with which BAL detects infection (defined as a positive culture)									
20*	Case series†	Serious‡	Serious§	None‖	Serious¶	Undetected	Not a prespecified outcome	Very low	Among the 20 case series identified, the proportion of BAL samplings that resulted in a positive microbiological culture ranged from 14 to 80%; however, most series reported that 40–60% of BAL samplings resulted in a positive microbiological culture. None of the series reported complications from BAL.
Frequency of wheezing after treatment									
1**	RCT	Serious††	Serious‡‡	None	Serious¶	Undetected	Critical	Very low	50 children with wet cough due to presumed bacterial bronchitis were treated with either antibiotics or no antibiotics. Among the patients who were treated, the cure rate was 48%. Among the patients who were not treated, the cure rate was 16%.

Definition of abbreviations: BAL = bronchoalveolar lavage; RCT = randomized controlled trial.

*References 6, 10, 12, and 44–61.

†No studies included a control group. Therefore, they are all case series.

‡Limitations were serious because of probable selection bias related to who underwent BAL and who did not. Most studies did not provide details of how they decided when to perform bronchoscopy with BAL and when not to perform bronchoscopy with BAL.

§Indirectness was serious because few studies were limited solely to wheezing infants. Most included older children and frequently cough overlapped with wheezing.

‖Inconsistency was not a problem. In most studies, the prevalence of positive BAL cultures was 40–60%.

¶Imprecision was serious because the sample size was small (<100) in all the studies that were reviewed.

**Reference 71.

††Descriptions of the concealment of allocation and blinding of the assessors were incomplete.

‡‡Indirectness was serious because the population of interest is wheezing infants, but the population studied was children with cough. In addition, the outcome of interest was wheezing, but the outcome of the studies was cure of infection.

with their associated risks, such as fever, rash, anaphylaxis, acquisition of resistance, and change in gut microbiome [72]) or third option (i.e., only 6.4–9.6% infection cure rate). The committee recognized that the estimated cure rates for lower respiratory infection likely overestimate the cure rate for wheezing because some infants with lower respiratory tract bacterial infection have additional or alternative causes of wheezing; nonetheless, the committee still thought that the risk of BAL is sufficiently small that the benefits probably outweigh the burdens and harms.

The strength of the recommendation for BAL is conditional because the committee's very low confidence in the estimated effects of BAL made it impossible to be certain that the benefits of BAL outweigh the risks and burdens in the majority of patients. Moreover, BAL requires bronchoscopy, an invasive procedure requiring sedation, and it is uncertain that most families would want bronchoscopy performed on their infant, despite persistent wheezing.

Recommendation 2. For infants with persistent wheezing despite treatment with bronchodilators, inhaled corticosteroids, or systemic corticosteroids, we suggest BAL (conditional recommendation, very low quality of evidence).

Question 3: Should Infants with Persistent Wheezing despite Treatment with Bronchodilators, Inhaled Corticosteroids, or Systemic Corticosteroids Be Managed according to the Results of Infant Pulmonary Function Testing Using the Raised-Volume Rapid Thoracoabdominal Compression Technique or Clinical Assessment Alone?

Summary of evidence. Our literature search revealed 1,261 studies related to wheezing and pulmonary function tests (PFTs) in children. The overwhelming majority (1,226 studies) were excluded because they enrolled children during later childhood, and the guideline development committee believed that such evidence was too indirect to inform judgments for infants. Among the 35 studies that involved PFTs performed during infancy, only 2 (from the same cohort of patients at two different time points) described clinical outcomes after the assessment of bronchodilator responsiveness (BDR) using the RVRTC technique (73, 74). Both studies reported that the presence of BDR identified by the RVRTC technique predicted future acute exacerbations of wheezing requiring treatment with systemic corticosteroids. No studies were identified that compared the effects of management according to the BDR measured by the RVRTC technique versus management based on clinical assessment alone (i.e., no PFTs) on the clinical outcomes of interest (frequency of wheezing, frequency of doctor visits, frequency of hospitalization, prescriptions for bronchodilators, prescriptions for inhaled or systemic corticosteroids, parental stress, additional diagnostic testing, and inappropriate therapy). Thus, there was no published evidence available to inform the guideline development committee's judgments.

Rationale. In the absence of published evidence, the guideline development committee turned to its collective clinical experience to try to answer the question. However, despite extensive discussion, the guideline development committee could not reach consensus on a clinical recommendation for or against infant PFTs, due to the paucity of evidence. Some members of the committee believed that the information derived from infant PFTs did not justify the burdens and risks involved in performing the test. Among the potential benefits of confirming or excluding BDR, the clinician may be directed away or toward diagnostic testing that targets anatomical causes of wheezing, respectively. Among the risks and burdens of such testing are the need for sedation; the risks associated with airway occlusion, gastric distention, and aerophagia; the additional personnel needed to monitor the infant during and after the test; and the time and personnel needed to set up and conduct the test. Other members of the guideline development committee believed that there are circumstances in which infant PFTs are clinically useful. For example, a restrictive pattern on the PFT might lead clinicians to explore interstitial lung disease, and marked gas trapping might motivate clinicians to evaluate the infant further for neuroendocrine hyperplasia of infancy, although wheezing is usually not a common feature of this condition (75).

Recommendation 3. In infants with persistent wheezing despite treatment with bronchodilators, inhaled corticosteroids, or systemic corticosteroids, we recommend research studies that compare clinical outcomes among infants who are managed according to infant PFT performed using the RVRTC technique versus those who are managed according to clinical assessment alone.

Question 4: Should Infants without Eczema Who Have Persistent Wheezing despite Treatment with Bronchodilators, Inhaled Corticosteroids, or Systemic Corticosteroids Undergo Empiric Food Avoidance?

Summary of evidence. The National Institute of Allergy and Infectious Diseases has published clinical guidelines on food allergy in children with eczema, including recommendations for food allergy testing and avoidance in infants and children with this condition (76). Therefore, we focused our question on the role of food avoidance in infants without eczema. Our systematic review identified four studies that assessed the results of empiric food avoidance (Table 3). All of the studies measured our prespecified outcome of frequency of wheezing, but none measured any of our other prespecified outcomes, including frequency of doctor visits, frequency of hospitalization, prescriptions for bronchodilators, prescriptions for inhaled or systemic corticosteroids, parental stress, additional diagnostic testing, and inappropriate therapy. A trial randomly assigned 487 infants to receive either a cow's milk–free diet or a usual diet for at least the initial 4 months of life and found no difference in wheezing, eczema, or nasal discharge at 1 year (77). Four hundred and forty-six of the infants were reassessed 6 years later. There were still no differences in the incidence of wheezing, asthma diagnoses, eczema, or allergic rhinitis (78). Another trial randomly assigned 110 infants to receive either a partially hydrolyzed formula or standard infant formula for the first 4 months of life. There was no difference in the incidence of wheezing at 2 years, although eczema was more common among the infants who received a standard formula (79). Finally, a prospective cohort study monitored 6,905 newborns through preschool age and found no relationship between the early introduction of potentially allergenic foods (e.g., cow's milk, egg, nuts, soy, or gluten) and either wheezing or eczema at

Table 3. Empiric Food Avoidance: Quality Assessment and Summary of Findings

Quality Assessment									
No.	**Study Design**	**Limitations**	**Indirectness**	**Inconsistency**	**Imprecision**	**Publication Bias**	**Importance of Outcome**	**Quality of Evidence**	**Summary of Findings**
Incidence of wheezing (measured at 1 yr)									
1	RCT*	Serious†	Serious‡	None	Serious§	None	Critical	Very low	The trial of 487 infants found no difference in the incidence of wheezing during the first year of life: 84/232 (36%) vs. 80/242 (33%)
Incidence of wheezing (measured at >1–4 yr)									
2	1 RCT‖ + 1 observational study¶	Serious**	Serious††	None	Serious§	None	Critical	Very low	The randomized trial of 110 infants found no difference in the incidence of wheezing at 2 yr The prospective cohort study of 6,905 children found no difference in the incidence of wheezing at 2, 3, or 4 yr among those who were introduced to cow's milk, nuts, egg, soy, or gluten earlier or later than 6 mo
Incidence of wheezing (measured at >4 yr)									
1	RCT‡‡	Serious§§	Serious‡	None	Serious§	None	Critical	Very low	The trial of 446 infants found no difference in the incidence of wheezing during the initial 7 yr of life: 148/215 (69%) vs. 157/231 (68%)
Diagnosis of asthma									
1	RCT‡‡	Serious§§	Serious‡	None	Serious§	None	Important	Very low	The trial of 446 infants found no difference in the incidence of asthma diagnoses during the initial 7 yr of life: 60/215 (28%) vs. 81/231 (35%)

Definition of abbreviation: RCT = randomized controlled trial.

*Reference 77.

†Concealment was by envelopes containing color-coded cards and the caregivers were not blinded.

‡The question is about infants without eczema who have refractory wheezing; however, the trial enrolled newborns. In addition, the question asks about general food avoidance, but the trial employed only cow's milk avoidance.

§The opposite ends of the confidence interval would result in different clinical decisions if real.

‖Reference 78.

¶Reference 79.

**The randomized trial did not report concealment and the caregivers were not blinded; the observational study relied on questionnaires that retrospectively assessed the introduction of certain foods into the diet, creating a risk of recall bias.

††The question is for infants without eczema who have refractory wheezing; however, the randomized trial enrolled newborns with a family history of atopy and the observational study monitored any newborn. In addition, the question asks about general food avoidance, but the trial employed only cow's milk avoidance.

‡‡Reference 80.

§§This was a 7-year follow-up of Miskelly and colleagues (77). Thus, it had the same limitations: Concealment was by envelopes containing color-coded cards and the caregivers were not blinded. In addition, 41 of the 487 patients dropped out of the study between Years 1 and 7.

ages 2, 3, and 4 years. The study plans to monitor the participants to adulthood (80). None of the studies evaluated the effects of empiric food avoidance in a subgroup of food antigen IgE–positive infants.

Taken together, the evidence suggests that empiric food avoidance has no effect on the frequency of wheezing. However, it provides very low confidence (i.e., quality of evidence) in the estimated effects because the randomized trials were limited by risk of bias, indirectness of population and intervention, and imprecision, and the observational study was limited by possible recall bias.

Rationale. The guideline development committee chose to include questions regarding food avoidance and allergy testing because in the collective experience of the committee, parents of infants with persistent wheezing frequently raise this topic. Although there is evidence that respiratory symptoms can be provoked by food antigens in infants with eczema (81), less is known about this relationship in infants without eczema. The guideline development committee's judgments were based on the impact of empiric food avoidance on frequency of wheezing, because our other prespecified outcomes were not reported. The lack of beneficial effects due to empiric food avoidance in any study, combined with the committee's recognition that empiric food avoidance can be burdensome, led the committee to suggest that empiric food avoidance not be used in infants without eczema who have persistent wheezing despite standard therapy. The strength of the recommendation is conditional because the very low quality of evidence prevented the committee from being certain about its judgments. In other words, although the committee believes that there is no evidence that the desirable consequences of empiric food avoidance outweigh the undesirable consequences in the majority of patients, it recognizes that there may be clinical circumstances in which a trial of empiric food avoidance may be reasonable for a minority of patients for whom the clinical history strongly correlates respiratory symptoms with food exposure or in whom respiratory symptoms are elicited in a double-blind placebo-controlled food challenge.

Recommendation 4.

A. For infants without eczema who have persistent wheezing despite treatment with standard therapies, we suggest *not* using empiric food avoidance (conditional recommendation, very low quality of evidence).
B. We recommend research to determine whether or not empiric food avoidance is beneficial for the subgroup of infants who are positive for IgE to food antigens.

Question 5: Should Infants with Persistent Wheezing despite Treatment with Bronchodilators, Inhaled Corticosteroids, or Systemic Corticosteroids Undergo 24-Hour Esophageal pH Monitoring?

Summary of evidence. Our systematic review did not identify any randomized trials or controlled observational studies that compared clinical outcomes among those who underwent 24-hour esophageal pH monitoring versus those who did not. However, we did identify three case series that used 24-hour pH monitoring to determine the prevalence of gastroesophageal reflux (GER) among children with wheezing and also reported the clinical outcomes that followed treatment of those with confirmed GER (Table 4) (82–84).

The most recent case series (83) enrolled 25 infants and children with asthma (88% had persistent wheezing) and performed 24-hour pH monitoring on all participants. GER was identified in 19 of 25 (76%) infants and children. Participants with GER were treated with a proton pump inhibitor and reassessed at 3 months, at which time there were statistically significant improvements in symptoms (from 2.3 to 0.4 symptoms per day), use of bronchodilators (from 8.3 to 1.4 d per patient), use of systemic steroids (from 5.3 to 0.4 d per patient), frequency of exacerbations (from 1.5 to 0.3 exacerbations per patient), and hospitalizations (from 9.1 to 0.5 d per patient) compared with before treatment.

The case series confirmed three earlier series. In the first (82), 36 infants and children with various respiratory disorders underwent 24-hour pH monitoring. GER was identified in 22 of 36 infants and children (61%) , including 4 of 6 infants and children (67%) with wheezing. Among those 22 patients, 9 patients underwent fundoplication, after which symptoms improved in 6 and resolved in 3. The remaining 13 patients with GER were treated with medical management; 9 had symptomatic improvement and 4 were lost to follow-up. In the second series (84), 12 infants with persistent wheezing despite bronchodilator and antiinflammatory therapy underwent 24-hour pH monitoring, and all were confirmed to have GER. They were subsequently treated with prokinetic agents and histamine receptor blockers; six improved enough to no longer require antiasthma medications, two improved enough that they required only intermittent antiasthma medications, and four failed to improve and underwent fundoplication. After fundoplication, three of the four patients no longer required antiasthma medications. In the third series (85), 81 children with recurrent pneumonias or chronic asthma underwent 24-hour pH monitoring, and 38 (47%) were found to have GER. Forty patients were treated for GER (2 on the basis of alternative tests). Among the 12 children who underwent medical management, 10 improved (83%). Among the 24 children who underwent surgical treatment, 22 improved (92%). Four patients were lost to follow-up. None of the case series reported any adverse effects from the 24-hour pH monitoring or subsequent therapy.

Taken together, the evidence indicates that GER exists in 47–100% of infants with persistent wheezing and, if identified, more than 83% (most estimates are in the 90–100% range) will improve with medical or surgical treatment. However, the evidence provides very low confidence in the estimated effects. With respect to indirectness of the population, most studies included older children with a mix of respiratory problems in addition to wheezing (e.g., recurrent pneumonia, apnea, stridor, and cough) and did not evaluate the wheezing infant subgroup. With respect to indirectness of the intervention, there was variability in the methods used for 24-hour pH monitoring, including positioning of probes, patient positioning, dietary restrictions, scoring criteria, definitions of an abnormal study, and use of impedance data. pH probes detect only acid reflux unless paired with impedance; thus, not using impedance data may underestimate episodes of postprandial reflux in infants with frequent feeds and buffering of gastric contents (86).

Table 4. Gastroesophageal Reflux: Quality Assessment and Summary of Findings

Quality Assessment									
No.	**Study Design**	**Limitations**	**Indirectness**	**Inconsistency**	**Imprecision**	**Publication Bias**	**Importance of Outcome**	**Quality of Evidence**	**Summary of Findings**
Frequency with which 24-h esophageal pH monitoring (gold standard) identifies GER									
4	Case series*	Serious†	Serious‡	None	Serious§	None	Not a prespecified outcome	Very low	24-h esophageal pH monitoring identified GER in 19/25 infants and children (76%),‖ 22/36 infants and children (61%),¶ 12/12 infants (100%),** and 38/81 children (47%).††
Wheezing									
4	Case series*	Serious†	Serious‡	None	Serious§	None	Critical	Very low	A case series of 25 infants and children with presumed asthma found GER in 19/25 (76%). After treatment of the GER, symptoms decreased from 2.3 to 0.4 symptoms per day and exacerbations decreased from 1.5 to 0.3 exacerbations per patient.‖ A case series of 36 infants and children with recurrent respiratory symptoms found GER in 22/36 (61%). Among those with GER, 9/22 (41%) underwent fundoplication with subsequent improvement or resolution in all, and 13/22 (59%) were medically managed with improvement in the 9 who were not lost to follow-up.¶ A case series of 12 infants with persistent wheezing found GER in 12/12 (100%); after treatment of the GER, 6/12 (50%) no longer needed medications for wheezing, 2/12 (17%) needed medications only intermittently, and 4/12 (33%) needed fundoplication, which eliminated the need for medications in 3/4 (75%).** A case series of 81 children with recurrent pneumonias or chronic asthma found GER in 38/81 (47%). Forty patients were treated for GER (2 on the basis of alternative tests). Among the 12 children who underwent medical management, 10 improved (83%). Among the 24 children who underwent surgical treatment, 22 improved (92%). Four patients were lost to follow-up.††

(Continued)

Table 4. (*Continued*)

No.	Study Design	Quality Assessment: Limitations	Indirectness	Inconsistency	Imprecision	Publication Bias	Importance of Outcome	Quality of Evidence	Summary of Findings
Use of bronchodilators									
1	Case series[||]	Serious[†]	Serious[‡‡]	None	Serious[§§]	None	Important	Very low	A case series of 25 infants and children with presumed asthma found GER in 19/25 (76%). After treatment of the GER, use of bronchodilators decreased from 8.3 to 1.4 d per patient.[||]
Use of systemic steroids									
1	Case series[||]	Serious[†]	Serious[‡‡]	None	Serious[§§]	None	Important	Very low	A case series of 25 infants and children with presumed asthma found GER in 19/25 (76%). After treatment of the GER, use of bronchodilators decreased from 5.3 to 0.3 d per patient.[||]
Hospitalizations									
1	Case series[||]	Serious[†]	Serious[‡‡]	None	Serious[§§]	None	Important	Very low	A case series of 25 infants and children with presumed asthma found GER in 19/25 (76%). After treatment of the GER, use of bronchodilators decreased from 9.1 to 0.5 d per patient.[||]

Definition of abbreviation: GER = gastroesophageal reflux.
*References 82–85.
[†]There was no process to ensure that patients were consecutively or randomly included; thus, selection bias in favor of infants clinically suspected of having GER is likely.
[‡]The question is specifically about infants with wheezing; however, three of the case series included older children and symptoms other than wheezing.
[§]There were only 154 patients in the four case series combined.
[||]Reference 83.
[¶]Reference 84.
[**]Reference 82.
[††]Reference 85.
[‡‡]The question is specifically about infants with wheezing; however, the case series included older children and asthma symptoms other than wheezing.
[§§]The case series included only 25 infants and children, of whom only 19 were treated for GER.

Rationale. The guideline development committee believed that the balance of benefits versus risks, burdens, and cost favors 24-hour pH monitoring in most infants who have persistent wheezing despite bronchodilator and antiinflammatory therapy. Specifically, among such infants who undergo 24-hour pH monitoring, 67–100% will be found to have GER and nearly all will improve substantially with treatment, without requiring further diagnostic testing. The procedure is well tolerated by the vast majority of patients and, although its semiinvasive nature and potential need for inpatient admission may be concerning to some parents, the committee believed that most families would be willing to have the test done. Although combined pH and impedance probe monitoring has become the standard at most centers, the available evidence largely predates widespread use of impedance probes. Therefore, the committee was unable to comment specifically on the value of impedance monitoring.

An alternative to 24-hour pH monitoring is an empiric trial of antiacid therapy. However, in up to one-third patients receiving empiric therapy, the antiacid therapy is inappropriate and incurs unnecessary cost, burden, and risk. In addition, the rate of treatment success is likely to be lower among empirically treated patients because those with GER that requires fundoplication may be incorrectly considered nonresponders. In that case, it may be presumed that GER is not a contributor and the parents may never be offered potentially curative surgical therapy. Furthermore, studies in older patients suggest that proton pump inhibitor therapy is linked to increased risk of pneumonia (87). Although a similar risk has not been reported in infants, a normal pH-monitoring study could potentially reduce any risks associated with proton pump inhibitor therapy.

The strength of our recommendation is conditional because the very low quality of evidence provided little confidence in the estimated benefits and harms reported by the case series. As a result, the committee could not be certain about its judgments regarding the balance of benefits versus harms, burdens, and cost.

Recommendation 5. For infants with persistent wheezing that is not relieved by bronchodilators, inhaled corticosteroids, or systemic corticosteroids, we suggest 24-hour esophageal pH monitoring (conditional recommendation, very low quality of evidence).

Question 6: Should Infants with Persistent Wheezing despite Treatment with Bronchodilators, Inhaled Corticosteroids, or Systemic Corticosteroids Undergo an Upper Gastrointestinal Series Rather Than 24-Hour Esophageal pH Monitoring?

Summary of evidence. The guideline development committee next asked whether an upper gastrointestinal (UGI) series is an acceptable alternative to 24-hour esophageal pH monitoring, which we considered the reference standard. Our systematic review did not identify any randomized trials or controlled observational studies that compared clinical outcomes among those who underwent a UGI series with those who underwent 24-hour esophageal pH monitoring. However, it did identify three studies that evaluated the accuracy of a UGI series in detecting GER in infants and children with wheezing (Table 4) (82, 85).

In the only study that used 24-hour pH monitoring as the reference standard, 79 children (age, 2–17 yr) who had difficult-to-control asthma underwent 24-hour esophageal pH monitoring. GER was identified in 58 of 79 children (73%). A barium swallow study was then performed, which identified GER with a sensitivity and specificity of 46 and 82%, respectively (88).

The other two studies used various reference standards, but reported enough data to enable us to estimate the sensitivity of a UGI series in the detection of GER relative to 24-hour esophageal monitoring. In a study of infants and children (age, 2 mo–10.5 yr) with recurrent respiratory disorders (82), 22 of 36 (61%) were found to have GER by 24-hour pH monitoring, and 15 of 35 (42%) were found to have GER by UGI series. Assuming that patients in whom GER was detected by UGI series also had GER detected by 24-hour pH monitoring, the sensitivity of a UGI series would be 68%. In a study of 82 infants and children (5 mo–16 yr) with recurrent pneumonia or chronic asthma (85), 40 were found to have GER on the basis of study criteria; of these, 30 of 40 had positive UGI series results and 38 of the 39 infants who had 24-hour pH monitoring showed positive results (one patient did not undergo pH monitoring). On the basis of these numbers, the sensitivity of a UGI series would be 75%, compared with 97% for pH monitoring. The sensitivity of a UGI series appears to be similarly poor among children without respiratory symptoms (89).

These accuracy tests constitute very low-quality evidence, meaning that they provide very low confidence in their results. The poor quality of evidence reflects the fact that the studies did not enroll consecutive patients, and it was not reported whether there was legitimate uncertainty about the presence or absence of GER.

Rationale. The primary advantages of performing a UGI series rather than 24-hour esophageal pH monitoring are that a UGI series can be performed less invasively and in less time. A less frequent advantage is that UGI series occasionally demonstrate pertinent anatomical abnormalities, such as hiatal hernias or esophageal indentation suggestive of a vascular ring. The disadvantages of a UGI series include radiation exposure, the need for patient cooperation, and its semiinvasive nature.

The guideline development committee made the *a priori* decision that the benefits of a UGI series would outweigh both the disadvantages of a UGI series and the consequences of incorrect results if the false-negative rate was less than 10% (i.e., sensitivity greater than 90%) and the false-positive rate was less than 10% (i.e., specificity greater than 90%). In other words, assuming a prevalence of GER of roughly 60%, the committee would accept 40 false-positive results and 60 false-negative results for every 1,000 patients tested. The acceptable false-negative and false-positive rates are both relatively small because 24-hour pH monitoring is not overly risky or burdensome.

The evidence indicates that the sensitivity (68–79%) and specificity (82%) of UGI series are insufficient to warrant the use of UGI series as an alternative to 24-hour esophageal pH monitoring. The recommendation against UGI series is conditional because the very low quality of evidence does not provide sufficient confidence in the estimated sensitivity and specificity to be certain that a UGI series is not a worthwhile alternative. The meaning of a conditional recommendation is that it is right for most patients, but may not be right for a sizable minority

in certain situations. As an example, a UGI series can be a valuable tool for identifying vascular rings or slings and may be considered if such malformations are suspected. A UGI series can also be considered in circumstances in which 24-hour pH monitoring is not a practical option.

Recommendation 6. For infants with persistent wheezing that is not relieved by bronchodilators, inhaled corticosteroids, or systemic corticosteroids, we suggest 24-hour esophageal pH monitoring rather than a UGI series (conditional recommendation, very low quality of evidence).

Question 7: Should Infants with Persistent Wheezing That Is Not Relieved by Bronchodilators, Inhaled Corticosteroids, or Systemic Corticosteroids Undergo Gastroesophageal Scintigraphy Rather Than 24-Hour Esophageal pH Monitoring?

Summary of evidence. The guideline development committee next asked whether gastroesophageal scintigraphy is an acceptable alternative to 24-hour pH monitoring, which we considered the reference standard. Our systematic review did not identify any randomized trials or controlled observational studies that compared clinical outcomes among those who underwent scintigraphy with those who underwent 24-hour esophageal pH monitoring. However, it did identify four studies that evaluated gastroesophageal scintigraphic detection of GER in infants and children with wheezing.

In the only study that used 24-hour pH monitoring as the reference standard, 79 children (age, 2–17 yr) who had difficult-to-control asthma underwent 24-hour esophageal pH monitoring. Gastroesophageal scintigraphy identified GER with a sensitivity and specificity of 15 and 73%, respectively (88). Another study of infants with wheezing used clinical history and a response to anti-GER therapy as the reference standard instead of 24-hour pH monitoring. It found that gastroesophageal scintigraphy detected GER with a sensitivity and specificity of 58 and 85%, respectively, when a history compatible with GER was used as the reference standard, and with a sensitivity and specificity of 79 and 50%, respectively, when a response to anti-GER therapy was used as the reference standard (90). Finally, two studies did not compare gastroesophageal scintigraphy with a reference standard, but rather, reported that the technique identified GER in 22% of infants and children (age, 3 mo–4 yr) who presented with recurrent wheezing or vomiting (91) and in 26% of infants and children (age, 6 mo–6 yr) who presented with difficult-to-treat asthma (92); these yields were lower than the 67–100% described previously for 24-hour esophageal pH monitoring. The sensitivity of gastroesophageal scintigraphy appears to be similarly poor among infants and children without respiratory symptoms (89).

These accuracy studies constitute very low quality of evidence, meaning that they provide very low confidence in their estimated effects. The poor quality of evidence reflects the fact that the studies did not enroll consecutive patients, and it was not reported whether there was legitimate uncertainty about the presence or absence of GER. Moreover, there was indirectness of the population because our focus was on wheezing infants, but many of the studies enrolled older children.

Rationale. The primary advantages of gastroesophageal scintigraphy rather than 24-hour esophageal pH monitoring are that scintigraphy can be performed less invasively and in less time. The disadvantages of scintigraphy are primarily radiation exposure (albeit less than that required for a UGI series) and high cost.

The guideline development committee made an *a priori* decision that the advantages of gastroesophageal scintigraphy would outweigh the disadvantages associated with potential incorrect results if the false-negative rate was less than 10% (i.e., sensitivity greater than 90%) and the false-positive rate was less than 10% (i.e., specificity greater than 90%). In other words, assuming a prevalence of GER of roughly 60%, the committee would accept 40 false-positive results and 60 false-negative results for every 1,000 patients tested. The acceptable false-negative and false-positive rates are both relatively small because 24-hour pH monitoring is not overly risky or burdensome.

The evidence indicates that the sensitivity and specificity (15 and 73%, respectively) of gastroesophageal scintigraphy are insufficient to warrant the use of scintigraphy as an alternative to 24-hour esophageal pH monitoring. The recommendation against scintigraphy is conditional because the very low quality of evidence does not provide sufficient confidence in the estimated sensitivity and specificity to be certain that scintigraphy is not a worthwhile alternative.

Recommendation 7. For infants with persistent wheezing that is not relieved by bronchodilators, inhaled corticosteroids, or systemic corticosteroids, we suggest 24-hour esophageal pH monitoring rather than gastrointestinal scintigraphy (conditional recommendation, very low quality of evidence).

Question 8: Should Infants without Neurologic Pathology with Persistent Wheezing That Is Not Relieved by Bronchodilators, Inhaled Corticosteroids, or Systemic Corticosteroids Undergo a Swallowing Function Study?

Summary of evidence. Our literature review did not identify any randomized trials or controlled observational studies that compared clinical outcomes among those who underwent a swallowing function study versus those who did not. However, it did identify two case series that reported the prevalence of aspiration detected by video-fluoroscopic swallowing function studies in infants and children who did not have chronic illnesses but did have respiratory symptoms including wheezing (Table 5). Both series also reported the outcomes of treatment (93, 94).

The first series enrolled 472 infants (age, $<$1 yr) with either respiratory symptoms or vomiting and performed fluoroscopic swallowing studies on each. Swallowing dysfunction was detected in 63 of 472 infants (13%). Among these infants, 70% had tracheal aspiration and 30% had laryngeal penetration. Because the coordination of swallowing improves with age among infants without chronic illnesses, the infants with swallowing dysfunction were managed by thickening the consistency of their food. Tracheal aspiration or laryngeal penetration was seen in 179 swallowing studies with thin liquids, 61 studies with thickened liquids, and 14 studies with pureed food (93).

The second case series included 112 infants (age, $<$1 yr) with wheezing or intermittent stridor and performed video-

Table 5. Aspiration: Quality Assessment and Summary of Findings

Quality Assessment									
No.	**Study Design**	**Limitations**	**Indirect-ness**	**Inconsistency**	**Imprecision**	**Publication Bias**	**Importance of Outcome**	**Quality of Evidence**	**Summary of Findings**
Frequency with which video-fluoroscopic swallowing studies (gold standard) identify aspiration due to swallowing dysfunction									
2	Case series*	Serious†	Serious‡	None	Serious§	None	Not a prespecified outcome	Very low	472 infants (age less than 1 yr) with either respiratory symptoms or vomiting underwent fluoroscopic swallowing studies; swallowing dysfunction was detected in 63 of 472 infants (13%)‖ 122 infants (age less than 1 yr) with either wheezing or intermittent stridor underwent fluoroscopic swallowing studies; swallowing dysfunction was detected in 13 of 112 infants (12%)¶
Wheezing (assessed by the surrogate outcome of radiographic tracheal aspiration or laryngeal penetration)									
2	Case series*	Serious†	Serious‡	None	Serious§	None	Critical	Very low	In a case series of 472 infants (age less than 1 yr) with either respiratory symptoms or vomiting, tracheal aspiration or laryngeal penetration was seen in 179 swallowing studies with thin liquids, 61 studies with thickened liquids, and 14 studies with pureed food, a risk reduction of more than 90%‖ In a case series of 122 infants (age less than 1 yr) with either wheezing or intermittent stridor, nine infants with confirmed swallowing dysfunction were treated with a thickened diet, while four infants had their oral feedings stopped and received nasojejunal or gastrostomy feedings temporarily. In all of the infants, the swallowing dysfunction resolved within 3–9 mo¶

*References 93 and 94.
†There was no process to ensure that patients were consecutively or randomly included; thus, selection bias in favor of infants clinically suspected of having swallowing dysfunction is likely.
‡The question is specifically about infants with wheezing; however, both case series included infants with symptoms other than wheezing.
§There were only 584 patients in the two case series combined.
‖Reference 93.
¶Reference 94.

fluoroscopic swallowing function studies on each. Swallowing dysfunction was detected in 13 of 112 infants (12%). Nine infants were treated with a thickened diet, and four infants had their oral feedings stopped and received nasojejunal or gastrostomy feedings temporarily. In all of the infants, the swallowing dysfunction resolved within 3–9 months (94).

Taken together, the evidence suggests that swallowing dysfunction, which is known to cause wheezing, can be identified by video-fluoroscopic swallowing studies in 10–15% of infants who do not have a chronic illness but have respiratory symptoms. More than 90% of such patients will improve with feeding interventions while waiting for the swallowing coordination to improve with age. Thus, 9–14% of patients who undergo video-fluoroscopic swallowing studies may derive some benefit. The committee has very low confidence (i.e., quality of evidence) in the accuracy of these estimated effects because the study designs were case series (i.e., they were uncontrolled); and there was risk for indirectness (i.e., most series looked at infants who had a variety of respiratory symptoms, not specifically wheezing).

Rationale. A video-fluoroscopic swallowing study confers several potential benefits. Finding swallowing dysfunction usually leads to feeding modifications that reduce aspiration by approximately 90%; a reduction in aspiration is a surrogate outcome for persistent wheezing, stridor, cough, and pneumonia. Other benefits include relief from the burden, cost, and potential harms of further diagnostic testing; probable reductions in the use of ineffective medications (bronchodilators or inhaled corticosteroids) and the frequency of physician visits; and parental reassurance given the high likelihood that the condition will spontaneously resolve. Limitations include the need for infant/child cooperation, cost, availability of speech pathologist, and the risk of aspiration during the study. The committee judged that the desirable consequences outweigh the undesirable consequences and, therefore, suggests that infants with persistent wheezing that has not responded to conventional therapies undergo a video-fluoroscopic swallowing study. The recommendation is conditional because the very low quality of evidence provides little certainty that the benefits of a video-fluoroscopic swallowing study exceed the burdens, costs, and harms.

Recommendation 8. For infants without neurologic pathology with persistent wheezing that is not relieved by bronchodilators, inhaled corticosteroids, or systemic corticosteroids, we suggest a swallowing function study to evaluate for aspiration (weak recommendation, very low quality of evidence).

Limitations and Future Directions

A common theme throughout our guideline development was the striking paucity of data regarding infantile wheezing. Despite how widespread and common this clinical problem is, we were unable to find any large clinical studies that used consistent case definitions and outcomes. Most of the studies cited were case series, providing the lowest quality of evidence on the GRADE scale. Given the frequency with which infantile wheezing occurs, there is an urgent need for more rigorous research to be conducted in this field.

Although we used the GRADE methodology, we rarely had patient-important outcomes that could be reliably linked to performance of the various diagnostic tests. As a result, we presumed that treatment strategies based on a positive test would provide therapeutic benefit to the patient, but this presumption and limited evidence reduced our ability to make strong recommendations.

One clear need for future research is to determine whether implementation of these tests actually leads to treatment that improves patient-important outcomes. Outcome measures should include both clinical responses and parental preferences, particularly regarding choices between diagnostic testing and empiric treatment. However, study design is complicated by the fact that a substantial fraction of infants with persistent wheeze not responsive to standard therapies have anatomic abnormalities that may not respond to any medical therapy. Routine incorporation of bronchoscopy into clinical trials could address this issue, but likely would be problematic given the relatively high costs and risks associated with this procedure.

This issue highlights the fact that many current tests involve substantial costs and/or risks that limit widespread use. Further research should address whether diagnosis could be achieved by less invasive tests, radiologic studies in lieu of bronchoscopy for anatomic abnormalities, or analysis of exhaled breath to detect markers of airway infection or reflux. Comparative effectiveness studies and the development of clinical pathways would also help clinicians better evaluate infants with persistent wheezing.

In summary, this document provides guidelines that further two goals of interest to the ATS. First, they will aid the pediatric generalist or respiratory specialist in the management of the infant with recurrent or persistent wheeze that does not respond to conventional therapies. Second, they will serve to identify the research needed to improve diagnosis and treatment of this vulnerable population. ■

This clinical practice guideline was prepared by an *ad hoc* subcommittee of the ATS Assembly on Pediatrics.

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